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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* JOHN C. BELL, NAHUM SONENBERG,
DAVID F. STOJDL, EARL G. BROWN, HAROLD L. ATKINS,
RICARDO M. MARIUS, BRIAN D. LICHTY,
and SHANE B. KNOWLES

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Appeal 2010-004413
Application 09/664,444
Technology Center 1600

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Before ERIC GRIMES, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to methods of reducing the viability of tumor cells by administering a virus to the cells. The Examiner entered two rejections for enablement.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

## STATEMENT OF THE CASE

Claims 1, 6-13, 19, 24-37, 64-77, 79, and 80 stand rejected and appealed (App. Br. 5). Claim 78 is also pending and has been objected to as being dependent on a rejected claim (*id.*). Claims 1 and 35, the independent claims, illustrate the appealed subject matter and read as follows:

> 1. A method of reducing the viability of a tumor cell, comprising administering to the tumor cell a virus, such that the virus is delivered to the tumor cell,
> wherein said virus is a vesicular stomatitis virus [VSV] and said tumor cell is a hematopoietic tumor cell and
> wherein the virus is contained in a cell infected with the virus and the administering comprises administering the virus-infected cell.
>
> 35. A method of reducing the viability of a tumor cell within a population of cells comprising administering a vesicular stomatitis virus to the population of cells, such that the virus is delivered to the population of cells,
> wherein the virus is contained in a cell infected with the virus and the administering comprises administering the virus-infected cell,
> wherein the population of cells comprises hematopoietic tumor cells and non-tumor cells and
> wherein the virus is able to selectively reduce the viability of the hematopoietic tumor cells.

The following rejections are before us for review:

(1) Claims 27-31 and 73-77, under 35 U.S.C. § 112, first paragraph, as lacking enablement due to failure to meet the biological deposit requirements (Ans. 3-4); and

(2) Claims 1, 6-13, 19, 24-37, 64-77, 79 and 80, under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the subject matter encompassed by the claims (Ans. 4-15).

THE DEPOSIT REJECTION

In the deposit rejection, aside from explaining what statements must accompany a biological deposit, the Examiner states only that it is "apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 [C.F.R. §] 1.808(a))" (Ans. 3).

Appellants contend that the Examiner "has only made conclusory statements related to these claims as not meeting the enablement requirement (without a biological deposit). The Examiner has not, as required, provided reasons or evidence why deposits are necessary" to enable the claimed invention (App. Br. 9, 13).

Appellants contend that, as evidenced by their use in at least seven prior art publications, the claimed viral strains were known in the art and readily available, and further urge that, given the nucleic acid and amino acid sequence information provided for the strains in the application's original disclosure, an ordinary artisan would be able to make and use the claimed strains (*id.* at 12, 13). Thus, Appellants reason, because the Examiner has not "provided a reasonable basis to believe that the biological materials are not readily available and will cease to be available during the enforceable life of the patent," the Examiner has not established that a biological deposit is necessary in the instant circumstances (*id.* at 12).

We conclude that Appellants have the better position.

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Thus, when rejecting claims due to the absence of a deposit of biological material, an "examiner should clearly indicate the statutory basis for the rejection *and the reasons that are relied upon by the examiner to conclude that the application does not comply with some requirement of 35 U.S.C. 112*" (MPEP § 2411.01 (emphasis added)). The MPEP further explains that this type of rejection "should be accompanied by evidence of [sic, or?] scientific reasoning to support the conclusion that a person skilled in the art could not make or use the invention defined in and commensurate with the claims without access to the specific biological material" (MPEP § 2411.01(A)).

In the instant case, the Examiner has not asserted nor alleged that any of the claimed strains is not available, nor has the Examiner put forth any evidence, or advanced any reasoning, why a skilled artisan would have been unable to practice the invention recited in the rejected claims, particularly given the sequence information provided in the original disclosure.

Rather, as Appellants point out, the Examiner simply states that, because the rejected claims require specific viral strains, a deposit is required, without providing any supporting argument or rationale (*see* Ans. 3). Absent some explanation, however, as to why a deposit is needed in this case to satisfy the enablement requirement, we are not convinced that the Examiner has met the burden required to sustain this rejection.

The Examiner's response to Appellants' arguments does not persuade us to the contrary. The Examiner urges that Appellants have not

demonstrated that the strains at issue "are available without restriction. Appellant's arguments illustrate that restrictions apply to the public availability. For instance, the Journal of Virology only requires that a 'biological' be made 'available in a timely fashion and at a reasonable cost to member of the scientific community for non-commercial purposes.'" (Ans. 16-17.)

Nonetheless, given that a number of the claimed strains have been used by different research groups over a number of years (*see* App. Br. 10, 41 (Evidence Appendix)), a preponderance of the evidence supports Appellants' contention that the strains are in widespread use, and therefore readily available. Further, as noted in MPEP § 2404.01:

> By showing that a biological material is known and readily available or by making a deposit in accordance with these rules, applicant does not guarantee that such biological material will be available forever. Public access during the term of the patent may affect the enforceability of the patent. Although there is a public interest in the availability of a deposited biological material during and after the period of enforceability of the patent, there should not be any undue concern about continued access to the public. . . . Unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement. The incentives provided by the patent system should not be constrained by the mere possibility that a disclosure that was once enabling would become non-enabling over a period of time through no fault of the patentee. *In re Metcalfe*, 410 F.2d 1378, 161 USPQ 789 (CCPA 1969).

The Examiner also argues that the Specification "does not disclose the sequence for the entire genomes of the recited VSV strains. . . .

Consequently, contrary to Appellant' assertion, the skilled artisan cannot 'make' the recited VSV strains" (Ans. 17).

Again, however, the Examiner does not explain *why* a skilled artisan, armed with extensive prior art information about VSV (*see, e.g.* App. Br. 10, 41 (Evidence Appendix)), and further provided with the nucleic acid and amino acid sequences encoding the claimed strains' proteins, would have had to undertake undue experimentation to practice the invention recited in Appellants' claims absent access to a deposit of the biological material recited in those claims.

In sum, we are not persuaded that the Examiner has advanced sufficient evidence or scientific reasoning to meet the burden required to sustain the deposit rejection of claims 27-31 and 73-77. We therefore reverse the Examiner's deposit rejection of those claims.

## THE SCOPE OF ENABLEMENT REJECTION

The Examiner rejected claims 1, 6-13, 19, 24-37, 64-77, 79, and 80 under 35 U.S.C. 112, first paragraph

> because the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs [sic] in immunodeficient mice, does not reasonably provide enablement for the utilization [of] attenuated VSV for the reduction of viability of all types of hemapoietic tumor cells to reduce the viability of a tumor cell in an immunocompetent animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

(Ans. 4.)

The Examiner initially notes that inventions in well characterized and predictable arts require less guidance or direction in the supporting disclosure than when the nature of the invention is less well known and more unpredictable (*id.* at 5 (citing *In re Fisher,* 427 F.2d 833, 839 (CCPA 1970))). The Examiner also notes that the MPEP "states that physiological activity can be considered inherently unpredictable. Thus, Appellant assumes a certain burden in establishing that inventions involving physiological activity are enabled" (*id.*).

The Examiner further notes that Appellants' claims encompass "methods of 'treating' tumor cells which reside in a mammalian host," finding in particular that "all the instant claims read on the *in vivo* treatment of hema[to]poietic tumor cells in humans" (*id.* at 6).

In contrast, the Examiner finds, the Specification only discloses in vitro activity of VSV against certain cell lines:

> [T]he instant claims are drawn to all forms of hematopoietic tumor cells, while the specification has demonstrated only two leukemia cell lines (MD7E and LI210), a couple of AML cell lines OCI/AML3 and AML5, one CML cell line (K-562) and a T-cell leukemia (MOLT-4) that are that are [sic] susceptible to VSV infection. VSV was shown to reduce the viability of only the AML, CML and T-cell leukemia cell lines.

(*Id.*)

The Examiner contends that the Specification's disclosure of VSV's in vivo activity is similarly limited: "[t]he specification teaches how to use VSV to reduce the viability of melanoma cell lines injected into immunodeficient mice to form xenographs [sic] and provides *in vitro* data showing effects of VSV infection on a several hematopoietic cell lines

(either with or without alpha interferon)" (*id.* at 8). The Examiner finds, however, that the Specification "does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to 'treat' hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims" (*id.*).

Applying the oft-cited factors of *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the Examiner cites a number of publications to characterize the state of the art, and reasons that, given the art-recognized general lack of a correlation between a therapeutic agent's in vitro activity and its tumor-inhibiting activity in vivo, and given the art-recognized inability of mouse cancer tumor models to predict a therapeutic agent's anticancer activity, Appellants' disclosure fails to support the full scope of the subject matter encompassed by the claims (*id.* at 7-15).

Thus, the Examiner concludes, "taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph" (*id.* at 14-15).

Appellants contend that the Examiner has not met the burden required to make a prima facie case of non-enablement (App. Br. 14). Appellants urge that the Examiner improperly focused on only the therapeutic embodiments encompassed by the claims, and further urge that a number of post-filing publications verified the Specification's assertions regarding VSV's capacity to reduce the viability of hematopoietic tumor cells (*id.* at 15-23).

Appellants argue that the articles cited by the Examiner to advance the concept that mouse xenograft tumors are not predictive of anticancer activity actually support the opposite conclusion (*id.* at 23-28). Thus, Appellants argue, even given the shortcomings of in vitro disease models, "it is undeniable that *in vitro* experiments continue to be performed and relied upon to identify treatments for *in vivo* use. If the rejection was correct that 'clinical correlations are generally lacking' . . ., *in vitro* experiments would not be as widely used as they are" (*id.* at 31-32 (citing (December 30, 2002, Office Action, page 6)).

Appellants therefore conclude that, taking into account all of the evidence of record, "one skilled in the art, upon review of Applicants' specification, would have been enabled at the time of filing to reduce the viability of a hematopoietic tumor cell(s) without undue experimentation, even in an individual such as a human, using methods that are the subject matter of the claims presented herein" (*id.* at 33).

While this is arguably a close case, we find that a preponderance of the evidence supports Appellants' position that the Examiner has not made a prima facie case of lack of enablement.

The Examiner bears the burden of establishing that practicing the full scope of the claimed subject matter would have required undue experimentation. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). Thus, as Appellants point out, it is well settled that when making an enablement rejection, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or

reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

In the instant case, claim 1 recites a method of reducing the viability of a hematopoietic tumor cell by administering to the tumor cell a VSV virus contained in another cell that is infected with the virus. Claim 32, which depends from claim 1, recites that the tumor cell is in a mammalian subject, and claim 33, which depends from claim 32, specifies that the subject is a human.

As the Examiner concedes (Ans. 6), the Specification discloses that VSV strains have activity against a number of cell lines encompassed by the claims, including two leukemia cell lines (MD7E and LI210), two AML [acute myelogenous leukemia] cell lines (OCI/AML3 and AML5), one CML [chronic myelogenous leukemia] cell line (K-562), and one T-cell leukemia (MOLT-4) cell line.

As Appellants point out, and the Examiner does not dispute, the Specification also discloses that VSV strains were capable of reducing melanoma xenograft tumors implanted in nude mice (Spec. 32-33 (Example 5 (direct administration to tumor)) and Spec. 50 (Example 25 (intravenous administration))).

We acknowledge the teachings in Jain,[1] Freshney,[2] and Dermer,[3] that, due to the differences between the test tube and living host environments, in

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[1] Rakesh K. Jain, *Barriers to Drug Delivery in Solid Tumors*, 271 SCIENTIFIC AMERICAN 58-65 (1994).
[2] R. IAN FRESHNEY, CULTURE OF ANIMAL CELLS, A MANUAL OF BASIC TECHNIQUE 4 (1983).
[3] Gerald B. Dermer, *Another Anniversary for the War on Cancer*, 12 BIO/TECHONOLOGY 320 (1994).

vitro activity can be a poor predictor of in vivo therapeutic efficacy. We also acknowledge Wang's[4] disclosure regarding the difficulty in inducing tumor regression despite the promise of epitope immunization against certain melanomas, as well as Saijo's[5] disclosure that phase III trials of target-based anticancer drugs have generally produced negative results, despite predicted activity at the preclinical phase. We further acknowledge the teachings in Gura,[6] Kelland,[7] Voskoglou-Nomikos,[8] Schuh,[9] Bibby,[10] and Peterson[11] that activity against mouse xenograft tumors is often not a good predictor of a drug's ultimate anticancer activity in humans.

The Examiner does not, however, point to any discussion in any of the cited references about the use of viruses as therapeutic agents, much less VSV. Thus, while the Examiner has shown that, viewed prospectively,

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[4] Ena Wang et al., *T-cell-directed cancer vaccines: the melanoma model*, 1 EXP. OPIN. BIOL. THER. 277-290 (2001).
[5] Nagahiro Saijo, *What are the reasons for negative phase III trials of molecular-target-based drugs?*, 95 CANCER SCI. 772-76 (2004).
[6] Trisha Gura, *Systems for Identifying New Drugs Are Often Faulty*, 278 SCIENCE 1041-42 (1997).
[7] L.R. Kelland, *"Of mice and men": values and liabilities of the athymic nude mouse model in anticancer drug development*, 40 EUR. J. CANCER 827-836 (2004).
[8] Theodora Voskoglou-Nomikos et al., *Clinical Predictive Value of the in Vitro Cell Line, Human Xenograft, and Mouse Allograft Preclinical Cancer Models*, 9 CLINICAL CANCER RESEARCH 4227-4239 (2003).
[9] JoAnn C. L. Schuh, *Trials, Tribulations, and Trends in Tumor Modeling in Mice*, 32 TOXICOLOGIC PATHOLOGY (Suppl. 1) 53-66 (2004).
[10] M.C. Bibby, *Orthotopic models of cancer for preclinical drug evaluation: advantages and disadvantages*, 40 EUR. J. CANCER 852-857 (2004).
[11] J.K. Peterson and P.J. Houghton, *Integrating pharmacology and in vivo cancer models in preclinical and clinical drug development*, 40 EUR. J. CANCER 837-844 (2004).

methods of treating cancer can be unpredictable, none of the evidence advanced by the Examiner goes to the specific category of active agent recited in Appellants' claims.

We are not persuaded that unpredictability in the art, in and of itself, demonstrates non-enablement.

Further, as Appellants point out, a number of the articles cited by the Examiner recognize that, despite certain shortcomings, in vitro cell lines and mouse tumor xenografts have predictive value in drug development. (*See, e.g.,* Kelland 827 abstract ("The xenograft model remains of value in current preclinical cancer drug development, especially when such studies give due consideration to [certain specified] variables and are based on sound mechanistic (e.g. status of the selected target in the chosen model) and pharmacological (e.g. use of formulated agent) principles."); *see also* Voskoglou-Nomikos 4227 ("[U]nder the right framework and when panels are used, the *in vitro* cell line and human xenograft models may be useful in predicting the Phase II clinical trial performance of cancer drugs.").)

We acknowledge that a mere plan or "germ of an idea" is insufficient to enable claims directed to methods of treating specific disorders. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (affirming judgment of non-enablement of claims to treating Alzheimer's where disclosure lacked in vitro test results and only proposed, but did not provide animal test results).

In contrast to the situation in the *'318 Patent* case, however, here Appellants have provided in vitro data against target tumor cells encompassed by the claims, and provided data showing that their active agents function against tumor cells in vivo. We are not persuaded that the

Examiner has met the burden of showing that an ordinary artisan informed by the data in the Specification would have doubted VSV's capacity to inhibit hematopoietic tumor cells in a human subject.

As noted above, while the Examiner has provided evidence of unpredictability in this art, the cited references nonetheless also suggest that in vitro and in vivo models can be of predictive value. As also noted above, the Examiner has not advanced any evidence specific to the claimed active agents, or similar ones, showing that practicing the full scope of the claimed invention would have required undue experimentation. *Compare*, *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1324 (Fed. Cir. 2005) (enablement rejection affirmed in view of substantial evidence specifically suggesting that skilled artisan would not have linked mechanism of target disorder to claimed active agent).

We acknowledge that the Specification does not contain a working example of treating a human patient having a hematopoietic tumor. However, "human trials are not required for a therapeutic invention to be patentable." *In re '318 Patent Infringement Litigation*, 583 F.3d at 1324; *see also In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (finding human trials unnecessary in reversal of how-to-use enablement rejection of claims directed to antitumor agents).

While we also acknowledge that the claims' scope may be relatively broad, a claim does not lack enablement merely because it encompasses inoperative embodiments. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

In sum, given the teachings in the Specification, and the absence of state-of-the-art evidence specific to the claimed viral therapeutic agent, or its

class of agents, we are not persuaded that any unpredictability inherent in this art demonstrates a lack of enablement. Accordingly, for the reasons discussed, we conclude that a preponderance of the evidence supports Appellants' position that the Examiner has not made a prima facie case of lack of enablement.

We therefore reverse the Examiner's scope rejection of claims 1, 6-13, 19, 24-37, 64-77, 79 and 80.

## SUMMARY

We reverse the Examiner's rejection of claims 27-31 and 73-77, under 35 U.S.C. § 112, first paragraph, as lacking enablement due to failure to meet the biological deposit requirements.

We also reverse the Examiner's rejection of claims 1, 6-13, 19, 24-37, 64-77, 79 and 80, under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

REVERSED

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